

CLINDAMYCIN PHOSPHATE INJECTION USP

WARNING

Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS AND USAGE section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. See WARNINGS section. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

DESCRIPTION

Clindamycin phosphate injection is a sterile, nonpyrogenic solution for intramuscular or intravenous use which contains clindamycin

phosphate, a water soluble ester of clindamycin and phosphoric acid.

Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

The chemical name of clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl- *trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L- *threo*- α -D-*galacto*-octopyranoside 2-(dihydrogen phosphate).

The molecular formula is $C_{18}H_{34}ClN_2O_8PS$ and the molecular weight is 504.96.

The structural formula is represented below:

Each mL contains the equivalent of 150 mg clindamycin,...

[Note: Include information as required by 21 CFR 201.100 (b)(5)(iii)]

CLINICAL PHARMACOLOGY

Biologically inactive clindamycin phosphate is rapidly converted to active clindamycin.

By the end of short-term intravenous infusion, peak serum levels of active clindamycin are reached. Biologically inactive clindamycin phosphate disappears rapidly from the serum; the average disappearance half-life is 6 minutes; however, the serum disappearance half-life of active clindamycin is about 3 hours in adults and 2½ hours in children.

After intramuscular injection of clindamycin phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in children. Serum level curves may be constructed from IV peak serum

levels as given in Table 1 by application of disappearance half-lives listed above.

Serum levels of clindamycin can be maintained above the *in vitro* minimum inhibitory concentrations for most indicated organisms by administration of clindamycin phosphate every 8 to 12 hours in adults and every 6 to 8 hours in children, or by continuous intravenous infusion. An equilibrium state is reached by the third dose.

The disappearance half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease.

No significant levels of clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges.

Serum assays for active clindamycin require an inhibitor to prevent *in vitro* hydrolysis of clindamycin phosphate.

**Table 1. Average Peak Serum Concentrations After
Dosing with Clindamycin Phosphate**

Dosage Regimen	Clindamycin mcg/mL	Clindamycin Phosphate mcg/mL
Healthy Adult Males (Post equilibrium)		
300 mg IV in 10 min q8h	7	15
600 mg IV in 20 min q8h	10	23
900 mg IV in 30 min q12h	11	29
1200 mg IV in 45 min q12h	14	49
300 mg IM q8h	6	3
600 mg IM q12h*	9	3
Children (first dose)*		
5-7 mg/kg IV in 1 hr	10	
3-5 mg/kg IM	4	
5-7 mg/kg IM	8	

*Data in this group from patients being treated for infection.

Microbiology: Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms:

Aerobic gram positive cocci, including:

Staphylococcus aureus (penicillinase and
Staphylococcus epidermidis non-penicillinase producing strains). When tested by *in vitro* methods, some staphylococcal strains originally resistant to erythromycin rapidly develop resistance to clindamycin.

Streptococci (except *Enterococcus faecalis*)
Pneumococci

Anaerobic gram negative bacilli, including:

Bacteroides species (including *Bacteroides fragilis* group and
Bacteroides melaninogenicus group)
Fusobacterium species

Anaerobic gram positive nonsporeforming bacilli, including:

Propionibacterium
Eubacterium
Actinomyces species

Anaerobic and microaerophilic gram positive cocci, including:

Peptococcus species
Peptostreptococcus species
Microaerophilic streptococci

Clostridia: Clostridia are more resistant than most anaerobes to clindamycin. Most *Clostridium perfringens* are susceptible, but other species, e.g., *Clostridium sporogenes* and *Clostridium tertium* are frequently resistant to clindamycin. Susceptibility testing should be done.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

***In vitro* Susceptibility Testing:**

Disk diffusion technique--Quantitative methods that require

measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure ¹ has been recommended for use with disks to test susceptibility to clindamycin.

Reports from a laboratory using the standardized single-disk susceptibility test ¹ with a 2 mcg clindamycin disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 17 mm or greater, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones of 15 to 16 mm, indicating that the tested organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Standardized procedures require the use of control organisms. The 2 mcg clindamycin disk should give a zone diameter between 24 and 30 mm for *S. aureus* ATCC 25923.

Dilution techniques - A bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) for clindamycin is not more than 1.6 mcg/mL. Organisms are considered moderately susceptible if the MIC is greater than 1.6 mcg/mL and less than or equal to 4.8 mcg/mL. Organisms are considered resistant if the MIC is greater than 4.8 mcg per mL.

The range of MIC's for the control strains are as follows:

S. aureus ATCC 29213, 0.06 to 0.25 mcg/mL.
E. faecalis ATCC 29212, 4.0 to 16 mcg/mL.

For anaerobic bacteria the minimum inhibitory concentration (MIC) of clindamycin can be determined by agar dilution and broth dilution (including microdilution) techniques. ² If MICs are not determined routinely, the disk broth method is recommended for routine use. THE KIRBY-BAUER DISK DIFFUSION METHOD AND ITS INTERPRETIVE STANDARDS ARE NOT RECOMMENDED FOR ANAEROBES.

INDICATIONS AND USAGE

Clindamycin phosphate injection is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin phosphate injection is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of antibiotic-associated pseudomembranous colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Clindamycin phosphate injection is indicated in the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, *Streptococcus pneumoniae*, other streptococci (except *E. faecalis*), and *Staphylococcus aureus*.

Skin and skin structure infections caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, and anaerobes.

Gynecological infections including endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection caused by susceptible anaerobes.

Intra-abdominal infections including peritonitis and intra-abdominal abscess caused by susceptible anaerobic organisms.

Septicemia caused by *Staphylococcus aureus*, streptococci (except *Enterococcus faecalis*), and susceptible anaerobes.

Bone and joint infections including acute hematogenous osteomyelitis caused by *Staphylococcus aureus* and as adjunctive therapy in the

surgical treatment of chronic bone and joint infections due to susceptible organisms.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

WARNINGS

See WARNING box. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis.³⁻⁷ Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants. (See PRECAUTIONS--Pediatric Use).

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General

Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Clindamycin phosphate should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Clindamycin phosphate should be prescribed with caution in atopic individuals.

Certain infections may require incision and drainage or other indicated surgical procedures in addition to antibiotic therapy.

The use of clindamycin may result in overgrowth of nonsusceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Clindamycin phosphate injection should not be administered intravenously undiluted as a bolus, but should be infused over at

least 10 to 60 minutes as directed in the DOSAGE AND ADMINISTRATION section.

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy (see OVERDOSAGE).

Laboratory Tests

During prolonged therapy periodic liver and kidney function tests and blood counts should be performed.

Drug Interactions

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

Pregnancy

Safety for use in pregnancy has not been established.

Nursing Mothers

Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for adverse reactions due to clindamycin in neonates (see **Pediatric Use**), the decision to discontinue the drug should be made, taking into account the importance of the drug to the mother.

Pediatric Use

When clindamycin phosphate injection is administered to newborns, infants, and children, appropriate monitoring of organ system functions is desirable.

Usage in Newborns and Infants

The product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants.

ADVERSE REACTIONS

The following reactions have been reported with the use of clindamycin.

Gastrointestinal: Antibiotic-associated colitis (see WARNINGS), abdominal pain, nausea and vomiting. An unpleasant or metallic taste occasionally has been reported after intravenous administration of the higher doses of clindamycin phosphate.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for treatment of serious reactions.

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Renal: Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

Hematopoietic: Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

Musculoskeletal: Rare instances of polyarthrititis have been reported.

Cardiovascular: Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration. (See DOSAGE AND ADMINISTRATION section)

OVERDOSAGE

Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

DOSAGE AND ADMINISTRATION

If diarrhea occurs during therapy, this antibiotic should be discontinued. (See WARNING box)

Adults: Parenteral (IM or IV Administration): Serious infections due to aerobic gram-positive cocci and the more susceptible anaerobes (NOT generally including *Bacteroides fragilis*, *Peptococcus* species and *Clostridium* species other than *Clostridium perfringens*):

600-1200 mg/day in 2, 3 or 4 equal doses.

More severe infections, particularly those due to proven or suspected *Bacteroides fragilis*, *Peptococcus* species, or *Clostridium* species other than *Clostridium perfringens*:

1200-2700 mg/day in 2, 3 or 4 equal doses.

For more serious infections, these doses may have to be increased. In life-threatening situations due to either aerobes or anaerobes these doses may be increased. Doses of as much as 4800 mg daily have been given intravenously to adults. See **Dilution and Infusion Rates** section below.

Single intramuscular injections of greater than 600 mg are not recommended.

Alternatively, drug may be administered in the form of a single rapid infusion of the first dose followed by continuous IV infusion as follows:

To maintain serum clindamycin levels	Rapid infusion rate	Maintenance infusion rate
Above 4 mcg/mL	10 mg/min for 30 min	0.75 mg/min
Above 5 mcg/mL	15 mg/min for 30 min	1.00 mg/min
Above 6 mcg/mL	20 mg/min for 30 min	1.25 mg/min

Neonates (less than 1 month): 15 to 20 mg/kg/day in 3 to 4 equal doses. The lower dosage may be adequate for small prematures.

Children (over 1 month of age): Parenteral (IM or IV) administration: 20 to 40 mg/kg/day in 3 or 4 equal doses. The higher doses would be used for more severe infections. As an alternative to dosing on a body weight basis, children may be dosed on the basis of square meters body surface: 350 mg/m²/day for serious infections and 450 mg/m²/day for more severe infections.

Parenteral therapy may be changed to clindamycin palmitate hydrochloride for oral solution or clindamycin hydrochloride capsules when the condition warrants and at the discretion of the physician.

In cases of β -hemolytic streptococcal infections, treatment should be continued for at least 10 days.

Dilution and Infusion Rates: Clindamycin phosphate must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg per mL. Infusion rates should not exceed 30 mg per minute. The usual infusion dilutions and rates are as follows:

<i>Dose</i>	<i>Diluent</i>	<i>Time</i>
300 mg	50 mL	10 min
600 mg	50 mL	20 min
900 mg	50 - 100 mL	30 min
1200 mg	100 mL	40 min

Administration of more than 1200 mg in a single 1 hour infusion is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Dilution and Compatibility: Physical and biological compatibility studies monitored for 24 hours at room temperature have demonstrated no inactivation or incompatibility with the use of clindamycin phosphate injection in IV solutions containing sodium chloride, glucose, calcium or potassium, and solutions containing vitamin B complex in concentrations usually used clinically. No incompatibility has been demonstrated with the antibiotics cephalothin, kanamycin, gentamicin, penicillin or carbenicillin.

The following drugs are physically incompatible with clindamycin phosphate: ampicillin sodium, phenytoin sodium, barbiturates, aminophylline, calcium gluconate, and magnesium sulfate.

The compatibility and duration of stability of drug admixtures will vary depending on concentration and other conditions.

Physico-Chemical Stability of Diluted Solutions of Clindamycin :

Room temperature: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or Lactated Ringer's Injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 16 days at 25 °C. Also, 18 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, in minibags, demonstrated physical and chemical stability for at least 16 days at 25 °C.

Refrigeration: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or Lactated Ringer's Injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 32 days at 4 °C.

IMPORTANT: This chemical stability information in no way indicates that it would be acceptable practice to use this product well after the preparation time. Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

Frozen: 6,9 and 12 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or Lactated Ringer's Injection in minibags demonstrated physical and chemical stability for at least eight weeks at -10 °C.

Frozen solutions should be thawed at room temperature and not refrozen.

HOW SUPPLIED

- Established name
- Strength
- Packaging
- Dosage form
- Special handling and storage recommendations

REFERENCES

1. Bauer, AW, Kirby, WMM, Sherris, JC, Turck, M: Antibiotic susceptibility testing by a standardized single disk method, *Am J Clin Path*, **45**:493-496, 1966. Standardized Disk Susceptibility Test, Federal Register **37**:20527-29, 1972.
2. National Committee for Clinical Lab. Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria-Second Edition; Tentative Standard. NCCLS publication M11-T2. Villanova, PA; NCCLS; 1988.
3. Bartlett JG, et al: Antibiotic associated pseudomembranous colitis due to toxin-producing *Clostridia*. *N Eng J Med* 298(10):531-534, 1978.
4. George RH, et al: Identification of *Clostridium difficile* as a cause of pseudomembranous colitis. *Br Med J* 6114:669-671, 1978.
5. Larson HE, Price AB: Pseudomembranous colitis presence of clostridial toxin. *Lancet* 8052/3:1312-1314, 1977.

Clindamycin Phosphate
Injection USP

Labeling Guidance
Revised May, 1992

6. Rifkin GD, Fekety FR, Silva J: Antibiotic-induced colitis implication of a toxin neutralized by *Clostridium sordellii* antitoxin. *Lancet* 8048:1103-1106, 1977.
7. Bailey WR, Scott EG: Diagnostic Microbiology. The CV Mosby Company, St. Louis, 1978.